

The cross product of two independently derived lists  
do not necessarily cover all clusters.

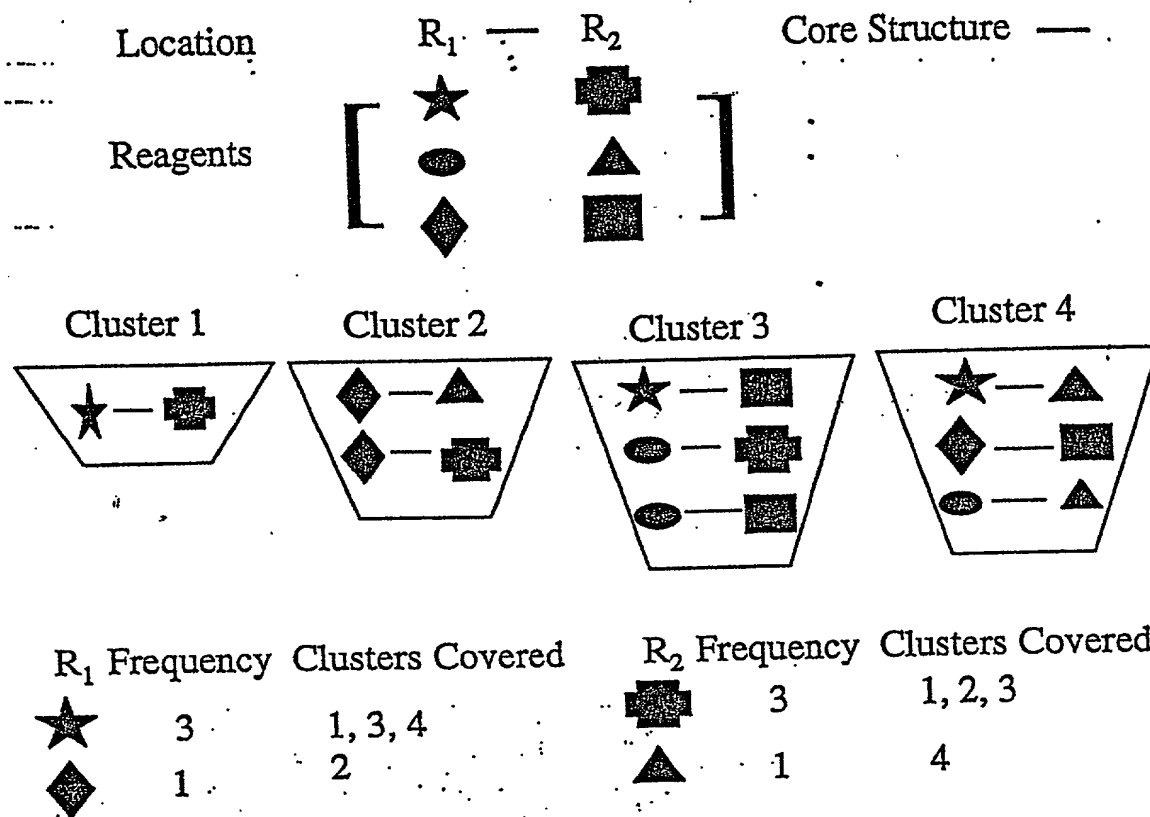


FIGURE 1

Example of Reactant Space for 3-R Group Combinatorial Library

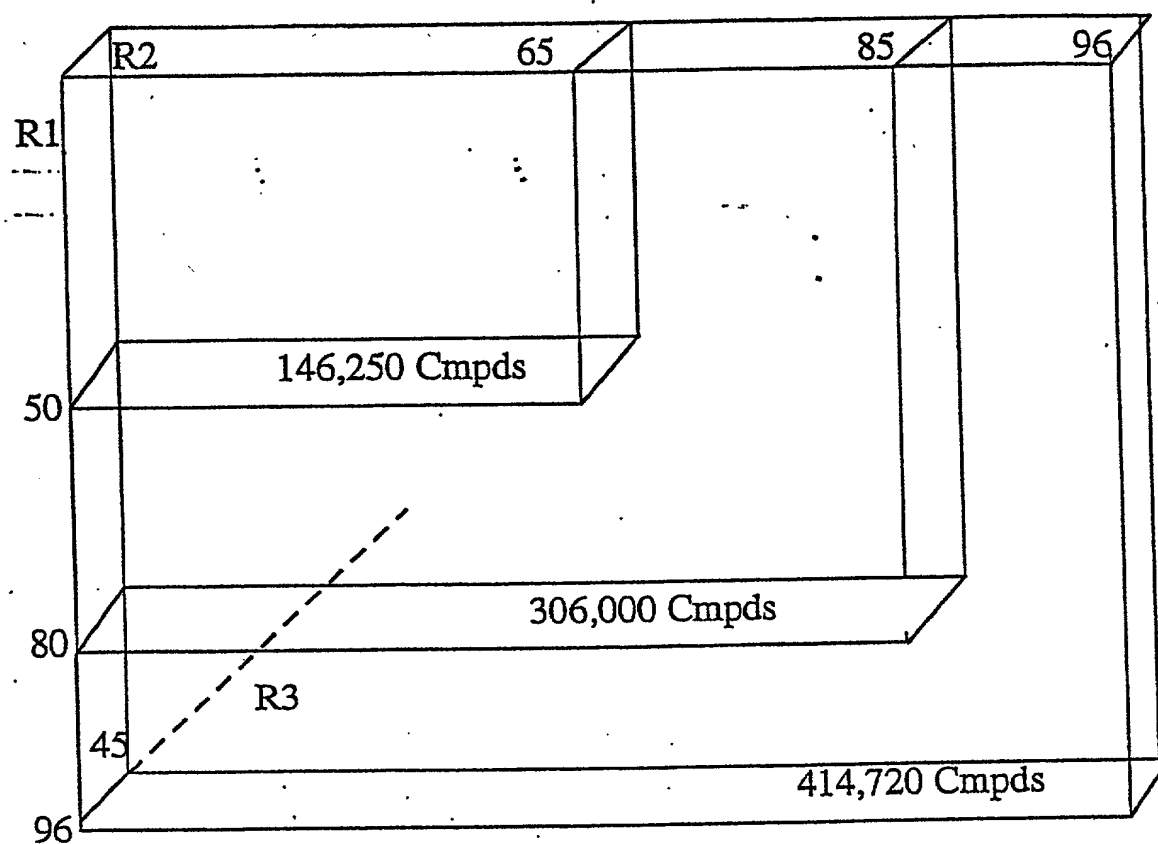
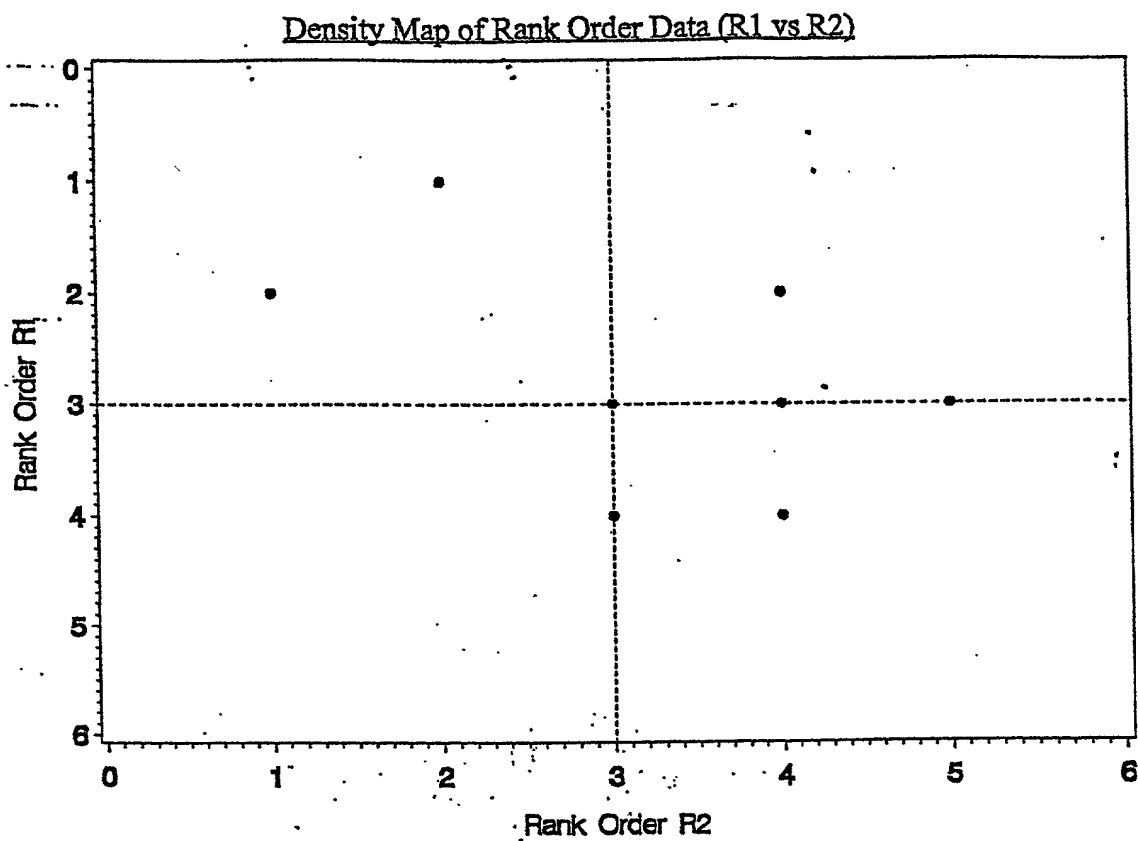


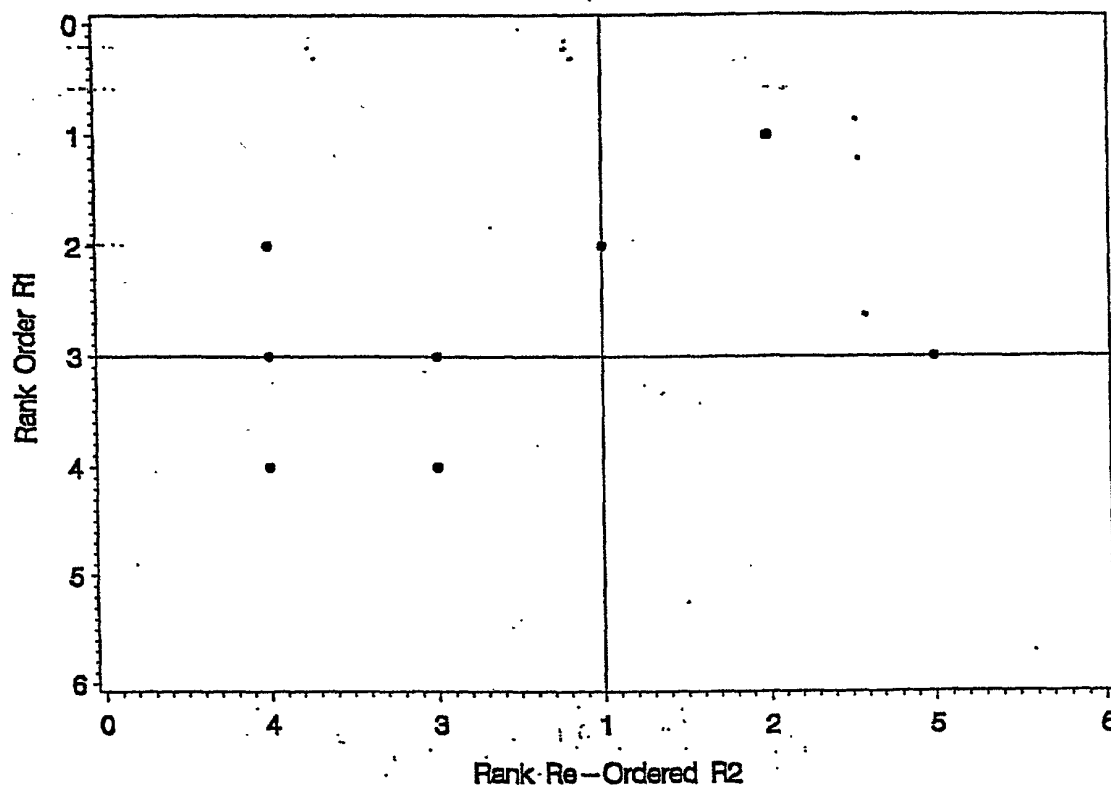
FIGURE 2



Note: 3 compounds in quadrant 1 (upper left), 3 compounds in quadrant 2 (upper right), 1 compound in quadrant 3 (lower left), and 1 compound in quadrant 4 (lower right).

FIGURE 3

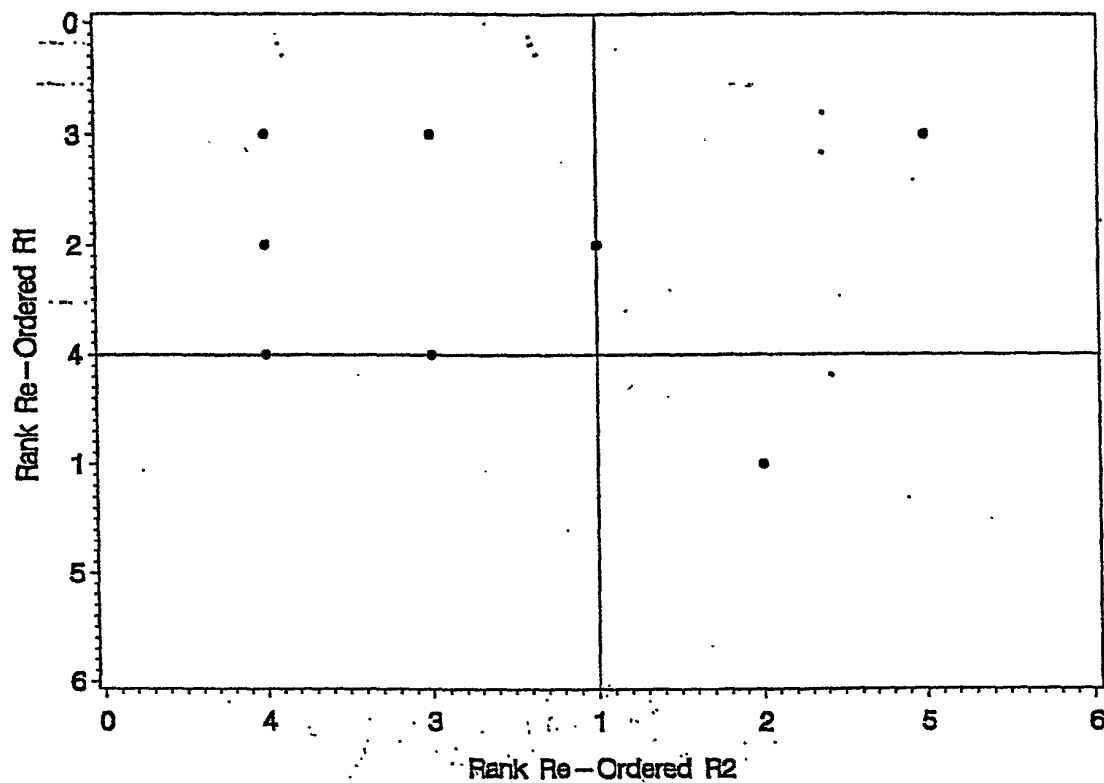
Column Reduced Density Map (R1 vs Re-Mapped R2)



Note: 4 compounds in quadrant 1 (upper left), 2 compounds in quadrant 2 (upper right), 2 compounds in quadrant 3 (lower left), and 0 compound in quadrant 4 (lower right).

FIGURE 4A

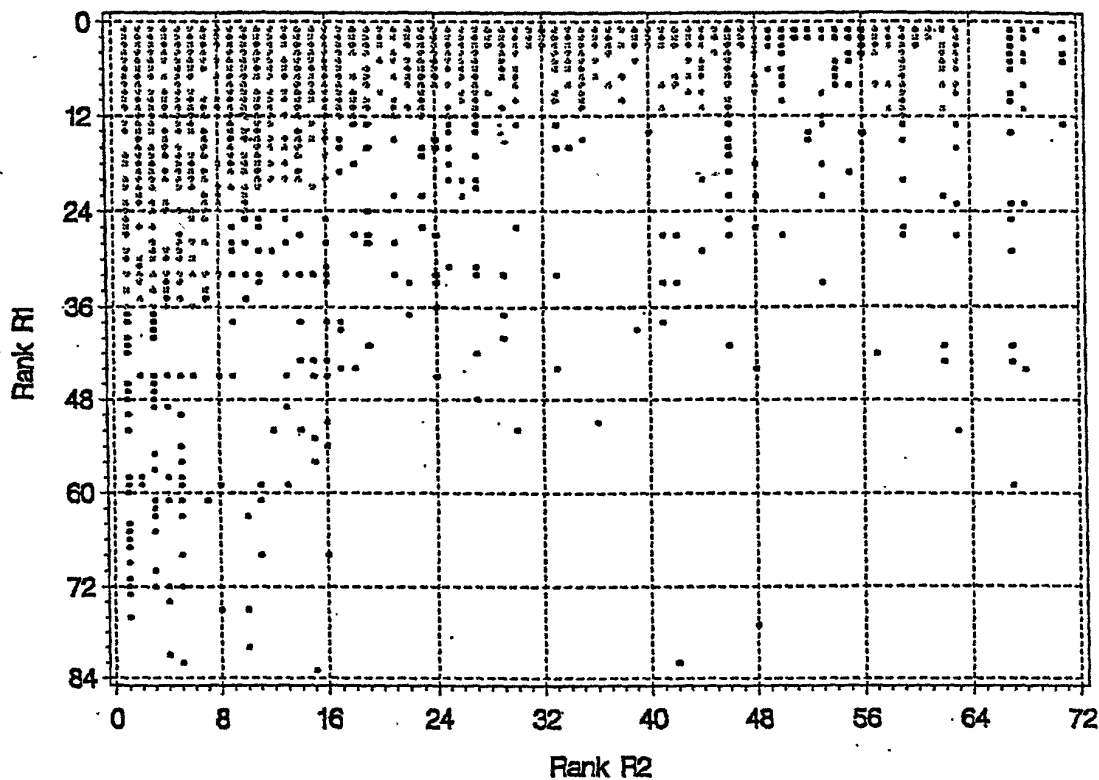
Column and Row Reduced Density Map (Re-Mapped R1 vs Re-Mapped R2)



Note: 6 compounds in quadrant 1, 1 compound in quadrant 2, and 1 compound in quadrant 4.

FIGURE 4B

Frequency Distribution Method 1 (No Plate Optimization)  
Density Map of 886 Clusters Ranked R1 vs Ranked R2 Reactants (substructures)  
 R1 contains 84 reactants and R2 contains 72 reactants (First 2 Lists).



Ten Most Dense ( $12 \times 8$ ) Plates Cover 597 Clusters  
 46 Plates Required to Cover All 886 Clusters

FIGURE 5A

# Frequency Distribution Method 1 (No Plate Optimization, 2 Lists)

Plate Frequency (12 × 8)

Plates are numbered 1-63 Left to Right, Top to Bottom

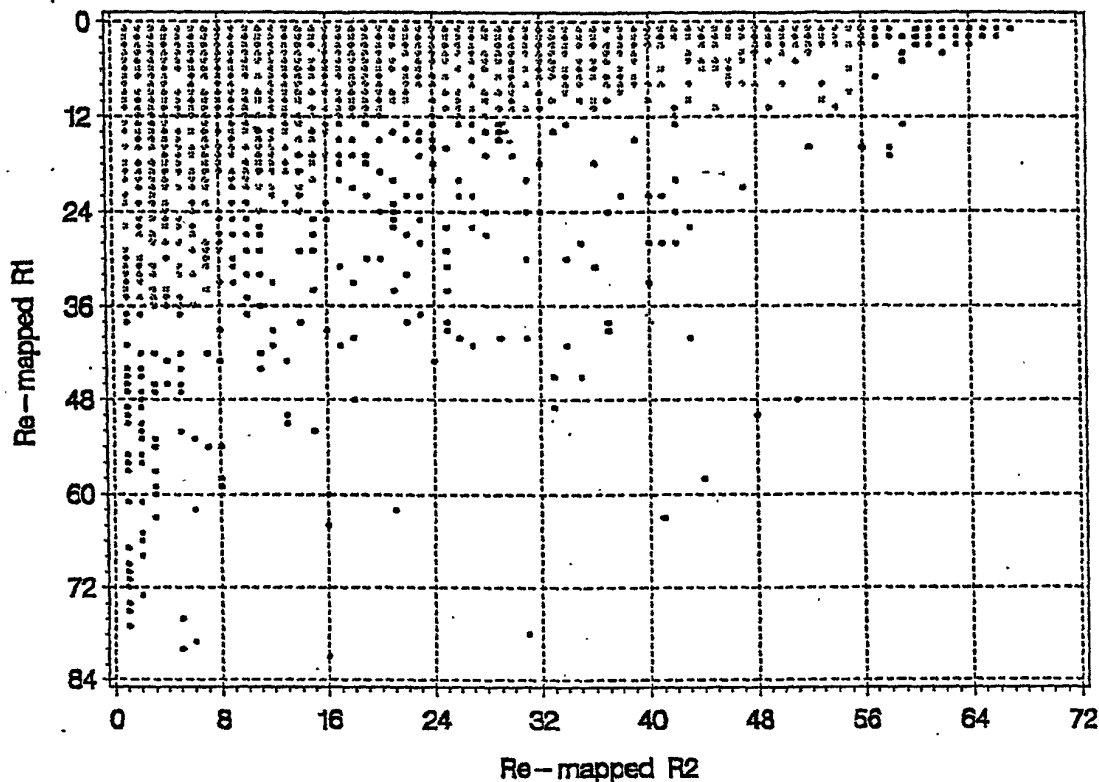
Number of Plates	Plate Number	Frequency Count	Percent Coverage	Clusters Covered
1	2	89	10.0451	89
2	1	83	9.3679	172
3	3	71	8.0135	243
4	10	67	7.5621	310
5	4	56	6.3205	366
6	6	48	5.4176	414
7	11	48	5.4176	462
8	5	47	5.3047	509
9	19	46	5.1919	555
10	8	42	4.7404	597
11	7	35	3.9503	632
12	20	25	2.8217	657
13	28	21	2.3702	678
14	46	20	2.2573	698
15	9	18	2.0316	716
16	37	18	2.0316	734
17	12	15	1.6930	749
18	13	13	1.4673	762
19	21	11	1.2415	773
20	29	10	1.1287	783
21	15	9	1.0158	792
22	38	9	1.0158	801
23	24	8	0.9029	809
24	16	7	0.7901	816
25	17	7	0.7901	823
26	30	7	0.7901	830
27	55	6	0.6772	836
28	14	5	0.5643	841
29	22	5	0.5643	846
30	18	4	0.4515	850
31	31	4	0.4515	854
32	47	4	0.4515	858
33	26	3	0.3386	861
34	33	3	0.3386	864
35	35	3	0.3386	867
36	36	3	0.3386	870
37	56	3	0.3386	873
38	25	2	0.2257	875
39	27	2	0.2257	877
40	32	2	0.2257	879
41	60	2	0.2257	881
42	23	1	0.1129	882
43	40	1	0.1129	883
44	41	1	0.1129	884
45	44	1	0.1129	885
46	45	1	0.1129	886

FIGURE 5B

### Frequency Distribution Method 1

#### Density Map of 886 Clusters Re-Ranked R1 vs Re-Ranked R2 Reactants

R1 contains 81 reactants and R2 contains 67 reactants (2 Lists).



Ten Most Dense (12 × 8) Plates Cover 636 Clusters

41 Plates Required to Cover 886 Clusters

Note: Although the R1 substituent count is 84 and the R2 substituent count is 72 for the total of the two lists, because substituent groups can be reselected in Method I, the actual number of unique substituents required to cover the 886 clusters is 81 for R1 and 67 for R2.

FIGURE 6A



# Frequency Distribution Method 1 (Plate Optimized, 2 Lists)

Plate Frequency (12 × 8)

Plates are numbered 1-63 Left to Right, Top to Bottom

Number of Plates	Plate Number	Frequency Count	Percent Coverage	Clusters Covered
1	1	91	10.2709	91
2	2	86	9.7065	177
3	3	80	9.0293	257
4	4	68	7.6749	325
5	10	68	7.6749	393
6	5	59	6.6591	452
7	11	55	6.2077	507
8	19	53	5.9819	560
9	6	42	4.7404	602
10	7	34	3.8375	636
11	12	31	3.4989	667
12	28	26	2.9345	693
13	8	24	2.7088	717
14	37	23	2.5959	740
15	20	22	2.4831	762
16	13	18	2.0316	780
17	46	12	1.3544	792
18	21	11	1.2415	803
19	29	8	0.9029	811
20	14	7	0.7901	818
21	22	7	0.7901	825
22	55	7	0.7901	832
23	30	6	0.6772	838
24	31	6	0.6772	844
25	9	5	0.5643	849
26	15	5	0.5643	854
27	23	5	0.5643	859
28	32	5	0.5643	864
29	38	4	0.4515	868
30	17	3	0.3386	871
31	24	3	0.3386	874
32	16	2	0.2257	876
33	42	2	0.2257	878
34	33	1	0.1129	879
35	34	1	0.1129	880
36	41	1	0.1129	881
37	47	1	0.1129	882
38	48	1	0.1129	883
39	51	1	0.1129	884
40	56	1	0.1129	885
41	58	1	0.1129	886

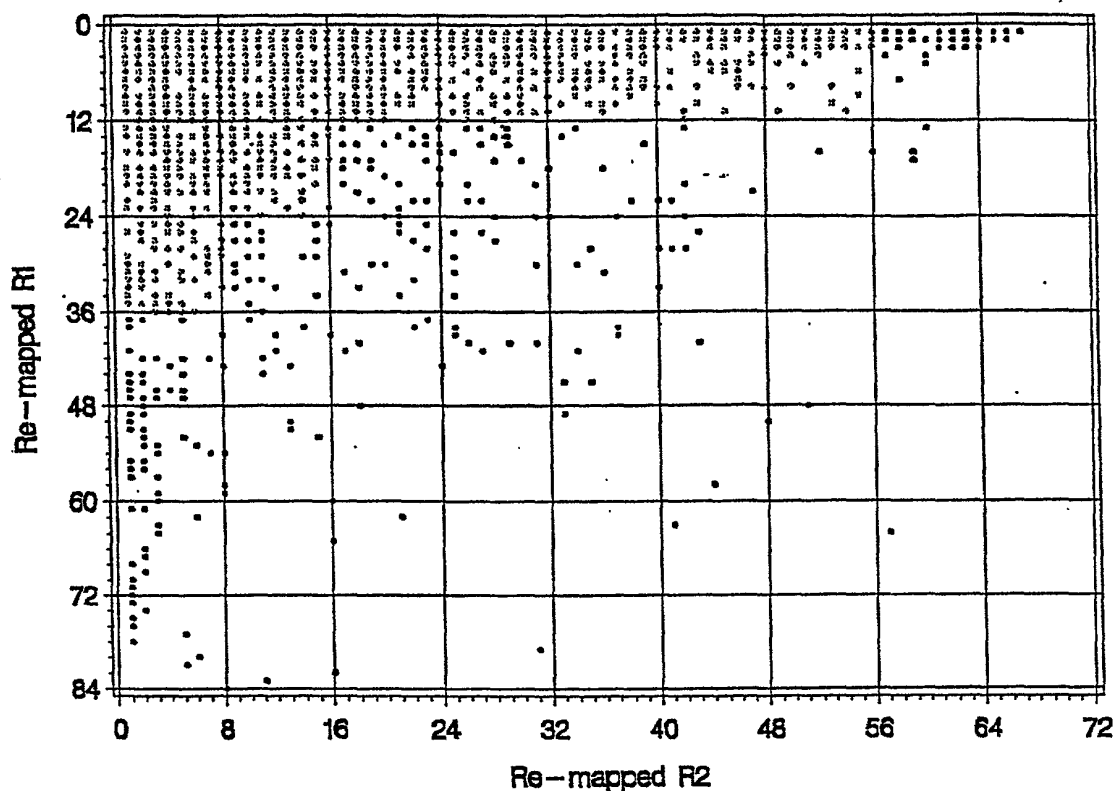
FIGURE 6B

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### Frequency Distribution Method 1

Density Map of 890 Clusters Re-Ranked R1 vs Re-Ranked R2 Reactants

R1 contains 84 reactants and R2 contains 67 reactants (3 Lists).



Ten Most Dense ( $12 \times 8$ ) Plates Cover 636 Clusters

42 Plates Required to Cover 890 Clusters

Note: Although the R1 substituent count is 92 and the R2 substituent count is 80 for the total of the three lists, because substituent groups can be reselected in Method I, the actual number of unique substituents required to cover the 890 clusters is 84 for R1 and 67 for R2.

FIGURE 7A

# Frequency Distribution Method 1 (Plate Optimized, 3 Lists)

## Plate Frequency (12 x 8)

Plates are numbered 1-63 Left to Right, Top to Bottom

Number of Plates	Plate Number	Frequency Count	Percent Coverage	Clusters Covered
1	1	91	10.2247	91
2	2	86	9.6629	177
3	3	80	8.9888	257
4	4	68	7.6404	325
5	10	68	7.6404	393
6	5	59	6.6292	452
7	11	55	6.1798	507
8	19	53	5.9551	560
9	6	42	4.7191	602
10	7	34	3.8202	636
11	12	31	3.4831	667
12	28	26	2.9213	693
13	8	24	2.6966	717
14	37	23	2.5843	740
15	20	22	2.4719	762
16	13	18	2.0225	780
17	46	12	1.3483	792
18	21	11	1.2360	803
19	55	9	1.0112	812
20	29	8	0.8989	820
21	14	7	0.7865	827
22	22	7	0.7865	834
23	30	6	0.6742	840
24	31	6	0.6742	846
25	9	5	0.5618	851
26	15	5	0.5618	856
27	23	5	0.5618	861
28	32	5	0.5618	866
29	38	4	0.4494	870
30	17	3	0.3371	873
31	24	3	0.3371	876
32	16	2	0.2247	878
33	42	2	0.2247	880
34	56	2	0.2247	882
35	33	1	0.1124	883
36	34	1	0.1124	884
37	41	1	0.1124	885
38	47	1	0.1124	886
39	48	1	0.1124	887
40	51	1	0.1124	888
41	53	1	0.1124	889
42	58	1	0.1124	890

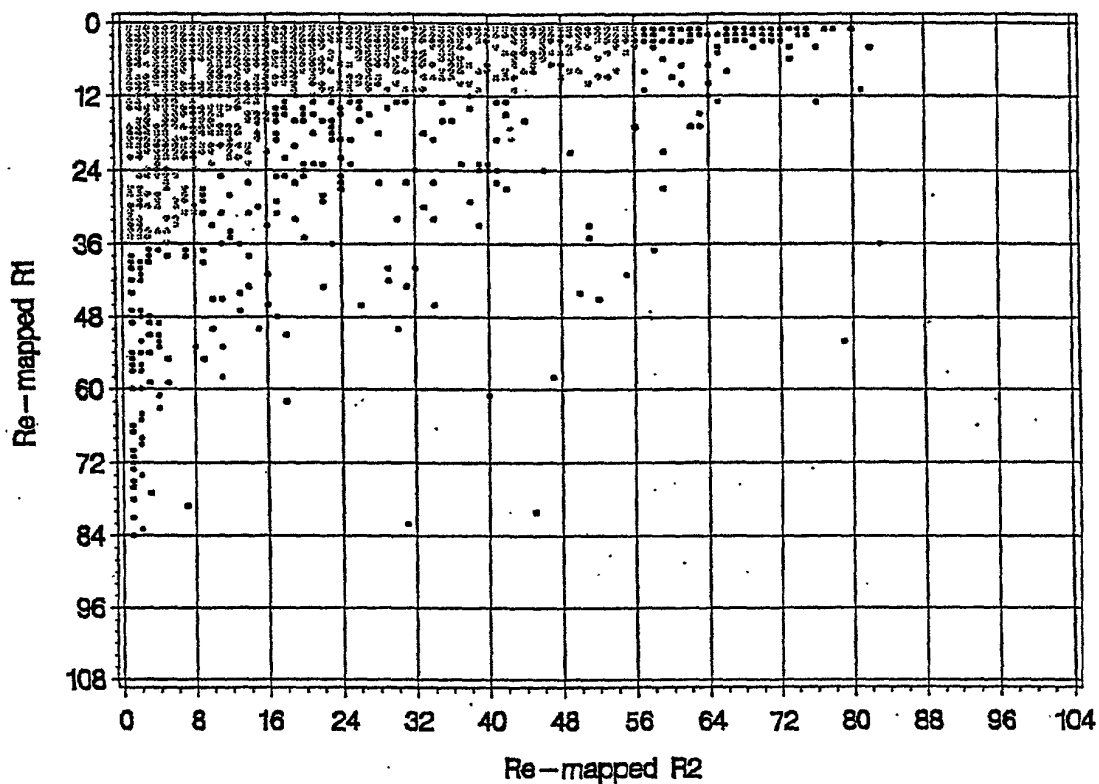
FIGURE 7B

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**Frequency Distribution Method 2**

**Density Map of 898 Clusters Re-Ranked R1 vs Re-Ranked R2 Reactants**

R1 contains 123 reactants and R2 contains 100 reactants.



Ten Most Dense ( $12 \times 8$ ) Plates Cover 620 Clusters  
49 Plates Required to Cover All 898 Clusters

FIGURE 8A

Frequency Distribution Method 2 (Plate Optimized, 6 Lists)

Plate Frequency (12 × 8)

Plates are numbered 1-117 Left to Right, Top to Bottom

Number of Plates	Plate Number	Frequency Count	Percent Coverage	Clusters Covered
1	2	90	10.0223	90
2	1	88	9.7996	178
3	14	73	8.1292	251
4	3	72	8.0178	323
5	4	68	7.5724	391
6	5	55	6.1247	446
7	15	47	5.2339	493
8	6	46	5.1225	539
9	27	44	4.8998	583
10	7	37	4.1203	620
11	16	31	3.4521	651
12	8	29	3.2294	680
13	9	25	2.7840	705
14	53	22	2.4499	727
15	40	20	2.2272	747
16	28	16	1.7817	763
17	29	14	1.5590	777
18	17	12	1.3363	789
19	10	11	1.2249	800
20	18	11	1.2249	811
21	66	11	1.2249	822
22	41	10	1.1136	832
23	79	10	1.1136	842
24	19	7	0.7795	849
25	31	5	0.5568	854
26	43	5	0.5568	859
27	54	5	0.5568	864
28	21	4	0.4454	868
29	30	3	0.3341	871
30	46	3	0.3341	874
31	11	2	0.2227	876
32	20	2	0.2227	878
33	32	2	0.2227	880
34	33	2	0.2227	882
35	42	2	0.2227	884
36	22	1	0.1114	885
37	23	1	0.1114	886
38	34	1	0.1114	887
39	37	1	0.1114	888
40	44	1	0.1114	889
41	47	1	0.1114	890
42	55	1	0.1114	891
43	56	1	0.1114	892
44	58	1	0.1114	893
45	62	1	0.1114	894
46	68	1	0.1114	895
47	70	1	0.1114	896
48	82	1	0.1114	897
49	84	1	0.1114	898

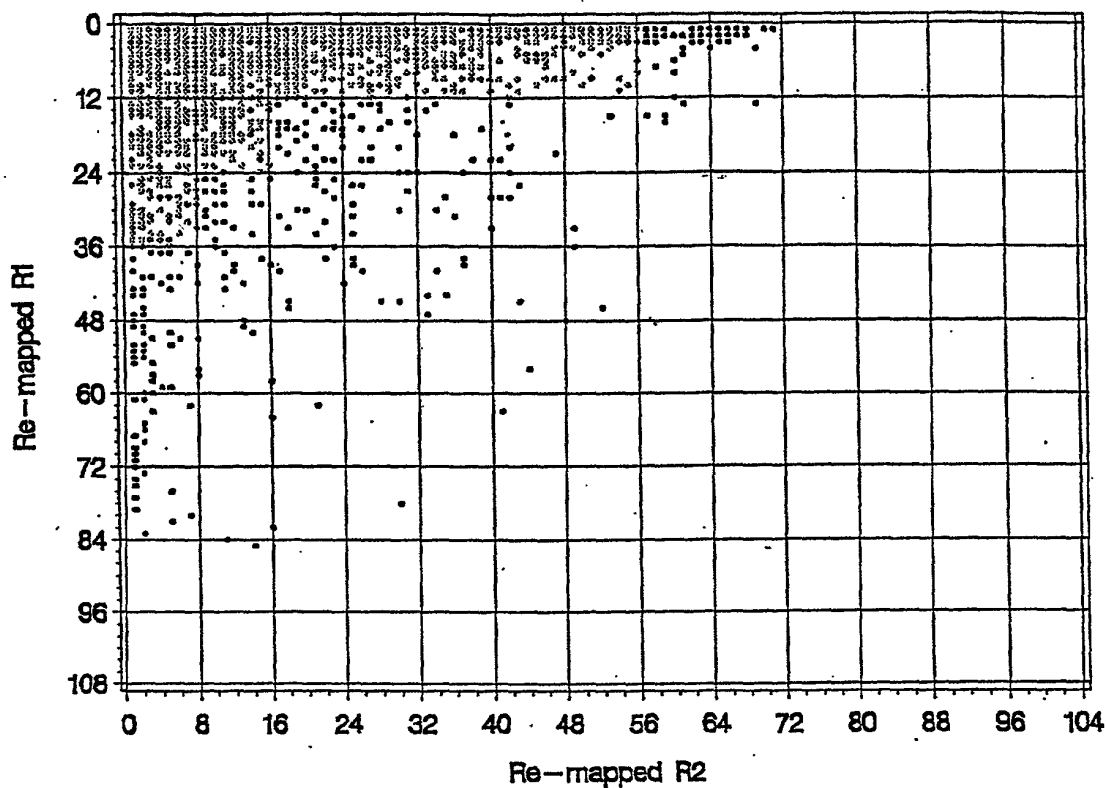
FIGURE 8B

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### Frequency Distribution Method 3

Density Map of 894 Clusters Re-Ranked R1 vs Re-Ranked R2 Reactants

R1 contains 96 reactants and R2 contains 78 reactants.



Ten Most Dense ( $12 \times 8$ ) Plates Cover 632 Clusters  
43 Plates Required to Cover 894 Clusters

FIGURE 9A

# Frequency Distribution Method 3 (Plate Optimized, 3 Lists)

Plate Frequency (12 × 8).

Plates are numbered 1-117 Left to Right, Top to Bottom

Number of Plates	Plate Number	Frequency Count	Percent Coverage	Clusters Covered
1	1	90	10.0671	90
2	2	86	9.6197	176
3	3	79	8.8367	255
4	4	67	7.4944	322
5	14	67	7.4944	389
6	5	59	6.5996	448
7	15	55	6.1521	503
8	27	52	5.8166	555
9	6	42	4.6980	597
10	7	35	3.9150	632
11	16	31	3.4676	663
12	8	25	2.7964	688
13	53	24	2.6846	712
14	28	22	2.4609	734
15	40	22	2.4609	756
16	17	18	2.0134	774
17	9	13	1.4541	787
18	29	12	1.3423	799
19	66	12	1.3423	811
20	41	9	1.0067	820
21	79	9	1.0067	829
22	18	7	0.7830	836
23	30	7	0.7830	843
24	44	6	0.6711	849
25	19	5	0.5593	854
26	31	5	0.5593	859
27	42	5	0.5593	864
28	43	5	0.5593	869
29	21	4	0.4474	873
30	32	3	0.3356	876
31	54	3	0.3356	879
32	33	2	0.2237	881
33	45	2	0.2237	883
34	80	2	0.2237	885
35	20	1	0.1119	886
36	22	1	0.1119	887
37	46	1	0.1119	888
38	58	1	0.1119	889
39	67	1	0.1119	890
40	68	1	0.1119	891
41	71	1	0.1119	892
42	82	1	0.1119	893
43	93	1	-0.1119	894

FIGURE 9B

Plate: 1 Layout (R1: PhEt) — Cluster ID (size,actives > 50%)  
 Activity (<50 50-59 60-69 70-79 80-89 >90)

R2

nBu	504(8,3)	215(24,1)	448(8,5)	88(21,0)	532(10,0)	3(23,1)	517(8,0)	491(9,0)
4dMaPh	329(8,1)	93(18,0)	357(18,2)	110(18,1)	373(17,0)	52(19,1)	359(14,0)	312(15,0)
4MeCOPh	232(17,10)	99(21,1)	245(19,2)	77(18,1)	251(15,0)	35(41,5)	256(19,3)	311(13,0)
3TMPH	374(23,10)	95(19,0)	369(13,1)	148(16,0)	426(15,0)	60(28,12)	361(13,1)	355(19,0)
3NOPh	106(25,12)	203(44,3)	543(13,3)	78(12,4)	570(13,0)	5(22,5)	558(13,1)	474(16,0)
3CIPh	189(13,8)	67(33,3)	195(13,1)	12(18,3)	305(13,1)	51(11,0)	206(13,1)	169(13,1)
2Pyr	394(6,2)	98(12,0)	403(6,2)	283(12,0)	324(6,0)	132(14,3)	405(6,0)	322(6,0)
2Naphth	331(11,4)	80(21,1)	356(27,3)	111(12,2)	352(23,0)	43(22,5)	366(25,1)	306(36,10)
2MOPh	73(29,4)	8(36,1)	142(28,7)	11(12,0)	223(16,0)	7(19,2)	149(29,2)	184(18,1)
2FPh	236(13,6)	47(20,0)	247(13,1)	17(9,0)	288(13,0)	20(18,0)	253(13,1)	231(13,0)

ALA ASP HIS HPHE LYS MPHE Thiof UPr

R3

FIGURE 10A

Plate: 2 Layout (R1: 4MoPh) — Cluster ID (size,actives > 50%)  
 Activity (<50 50-59 60-69 70-79 80-89 >90)

R2

nBu	446(20,3)	384(16,1)	209(9,0)	484(19,1)	610(13,0)	65(23,3)	183(9,4)	564(10,0)
4dMaPh	444(11,1)	94(35,5)	233(22,3)	451(23,5)	452(19,0)	56(19,3)	15(20,12)	440(15,1)
4MeCOPh	336(14,3)	147(25,0)	81(23,6)	389(14,8)	423(12,0)	122(14,5)	27(15,15)	402(14,1)
3TMPH	374(23,10)	48(31,3)	284(23,3)	515(18,11)	569(16,0)	102(14,4)	31(15,10)	527(17,1)
3NOPh	604(8,8)	121(21,2)	79(16,9)	349(32,24)	622(14,0)	4(22,16)	442(15,11)	582(16,0)
3CIPh	235(13,6)	62(8,2)	127(28,7)	244(15,5)	259(30,0)	159(12,3)	100(15,15)	154(30,1)
3COPh	219(10,1)	150(18,0)	186(13,9)	172(16,6)	644(12,0)	30(23,9)	26(13,8)	596(14,1)
2Naphth	501(19,6)	75(27,2)	237(30,12)	521(20,8)	557(25,0)	44(15,4)	14(21,16)	588(6,2)
2MOPh	297(9,1)	84(28,1)	19(18,9)	238(21,6)	313(22,0)	38(29,15)	4(22,16)	105(11,0)
2FPh	119(10,6)	101(15,0)	25(13,1)	187(18,8)	113(14,0)	115(14,4)	90(11,8)	109(10,0)

ALA ASP CHA LEU LYS MPHE NPHE UPr

R3

FIGURE 10B

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Plate: 13 Layout (R1: 24MoPh) — Cluster ID (size,actives > 50%)  
 Activity (<50 50-59 60-69 70-79 80-89 >90)

R2

PhMe	103(2,0)	181(17,0)	175(15,10)	19(18,9)	38(29,15)	4(22,16)	304(19,1)	105(11,0)
4MeCOPh	598(6,0)	273(26,5)	274(10,5)	81(23,5)	122(14,5)	27(15,15)	147(25,0)	402(14,1)
4AcNPh	594(7,0)	685(19,0)	277(25,3)	677(13,2)	575(15,0)	669(13,6)	320(7,0)	701(20,0)
3TMPH	289(8,0)	339(36,10)	60(28,12)	284(23,3)	102(14,4)	31(15,10)	48(31,3)	527(17,1)
3NOPh	234(13,4)	544(18,7)	28(24,13)	338(8,8)	4(22,16)	442(15,11)	121(21,2)	582(16,0)
3ClPh	271(10,0)	432(9,2)	439(9,6)	583(5,3)	437(9,6)	69(12,11)	138(17,1)	463(13,1)
3COPh	590(6,0)	594(7,0)	599(8,6)	186(13,9)	30(23,9)	26(13,8)	150(18,0)	596(14,1)
2Naphth	295(10,0)	553(7,0)	572(7,3)	237(30,12)	576(7,3)	588(5,5)	276(12,1)	607(7,2)

ASP AcLYS BzSER CHA MPHE NPHE SER UPr

R3

FIGURE 11A

Plate: 30 Layout (R1: EtAc) — Cluster ID (size,actives > 50%)  
 Activity (<50 50-59 60-69 70-79 80-89 >90)

R2

PhMe	430(22,5)	215(24,1)	585(19,0)
4dMaPh	484(19,1)	627(12,1)	585(19,0)
2MOPh	468(8,1)	384(16,1)	564(10,0)

LEU

SER

UPr

R3

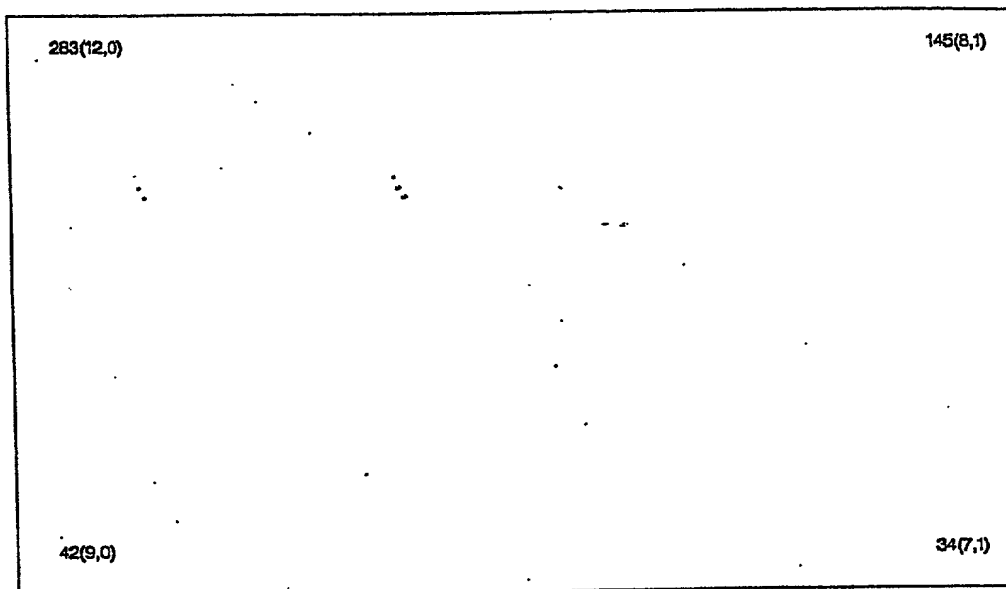
FIGURE 11B

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Plate: 31 Layout (R1: Ph) — Cluster ID (size,actives > 50%)  
 Activity (<50 50-59 60-69 70-79 80-89 >90)

R2

2Pyr



2MOPh

HPHE

MPHE

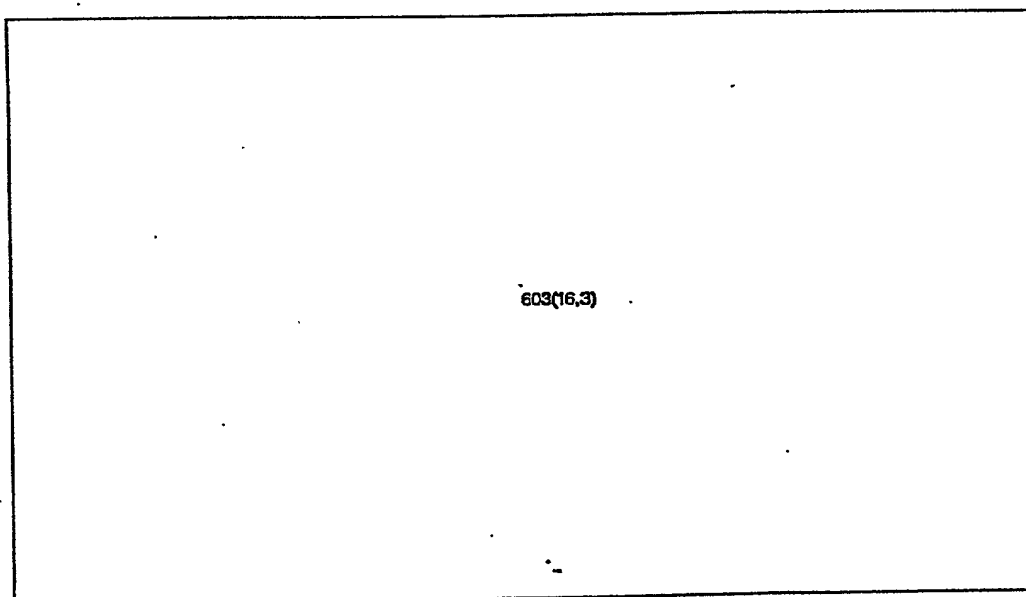
R3

FIGURE 12A

Plate: 33 Layout (R1: EtAc) — Cluster ID (size,actives > 50%)  
 Activity (<50 50-59 60-69 70-79 80-89 >90)

R2

4AcNPh



AcLYS

R3

FIGURE 12B.

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